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The Role of an Engineering Oriented Medical Research Group in Developing Improved Methods and Devices for Achieving Ventricular Defibrillation: The University of Missouri Experience

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SCHUDER, J.C.: The Role of an Engineering Oriented Medical Research Group in Developing Improved Methods and Devices for Achieving Ventricular Defibrillation: The University of Missouri Experience. *Physical scientists and engineers have played important roles in helping to expand our understanding of the factors that influence the defibrillation process and in developing improved methods and devices for achieving cardiac ventricular defibrillation. The long-term experience of one engineering oriented group, based in a clinical department of a medical school, is summarized. Emphasized are the features of a series of research defibrillators that facilitated the generation of an extensive experimental database from studies in dogs and calves, the development of the first automatic implantable defibrillator to be successfully used in dogs, and studies that furnished the rationale for the widespread use of the uniphasic truncated exponential waveform and for the increasing interest in a variety of biphasic and multiphasic waveforms. Also considered are studies concerning the scaling of the defibrillatory shock with subject size and the role of compound units, defibrillation threshold, and contour graphs in the presentation and interpretation of data. (PACE, Vol. 16, January, Part I 1993)*

transthoracic defibrillation, automatic implantable defibrillator, truncated exponential waveform, biphasic waveform, contour graph, scaling

Introduction

In June 1957 my wife, three children (ranging from < 1 to 10 years of age), and I piled into our 1950 Ford in Crete, Nebraska and headed by a somewhat roundabout route toward Philadelphia. Along the way, several days were spent visiting with the open heart surgery perfusion team and engineers at the Mayo Clinic. For me, the trip was more than just a geographic move nearly half way across the country; the move also represented a drastic shift in my career and career objectives from a path involving the more conventional applications of engineering, physics, and mathematics to their application to medicine.

From a background that included growing up with amateur radio, a B.S. in Electrical Engineering from the University of Illinois, industrial experience in the Electrophysics Department at the Westinghouse Research Laboratories in East Pittsburgh, being a commercial radiotelegraph operator on merchant ships, M.S. and Ph.D. degrees in Electrical Engineering (minors in physics and mathematics) from Purdue, and some 7 years teaching at Purdue and Doane College, I was going to a fellowship appointment in the Harrison Department of Surgical Research at the University of Pennsylvania. In my case, the career shift was quite deliberate and motivated almost entirely by growing reservations about the validity of spending one's working life in a portion of a professional field that was focusing to an inordinate extent upon educa-

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tion, research, and development in support of the cold war.

At Penn I became the "engineering member" of a small team that was then in the embryonic stage of building a viable clinical open heart surgery program using the heart-lung machine. In addition to being responsible for setting up the patient monitoring system and for designing improvements to our heart-lung apparatus, I was an intimate participant along with the rest of the team during clinical procedures and in the experimental studies that were carried out in support of the clinical program. Thanks to helpful cooperating cardiologists and anesthesiologists, as well as to those on our team, my 3-year tenure at Penn provided an excellent on-the-job training program!

It was at Penn that I became acutely aware of the range of cardiac related disease problems that might benefit from careful engineering—physical science input, my personal preference for more basic research rather than direct clinical oriented work, and the excessively long commuting time often associated with life in big cities.

Considerations such as these suggested one more move. This time, in June 1960, it was westward to Columbia, Missouri, a relatively small community with a medical school that had only recently returned to a 4-year program after an extended period as a 2-year school and one which, since it was still in its growth stage, gave promise of providing adequate laboratory space. Furthermore, there appeared to be administrative acceptance of the legitimacy of an engineering oriented medical research laboratory within a clinical department.

Initially focusing upon the problem of transmitting electromagnetic energy into the closed chest at levels anticipated to be needed for a totally implanted artificial heart (several tens of watts) our new group, in place in the Department of Surgery at the University of Missouri, quickly branched into other relevant areas.

Strongly supported and encouraged by Hugh E. Stephenson, Jr., a surgeon in the Department who had had a long-term interest in cardiac arrest and resuscitation, and motivated by an indication of interest in being an active participant in our studies by Harry Stoeckle, then a cardiologist in the Department of Pediatrics, we selected ventricular defibrillation as one of our areas of concentration.

This article is primarily concerned with the highlights of the first three decades or so of the continuing study of ventricular defibrillation by our engineering oriented group. An attempt is made to indicate how certain other investigators interacted with or motivated our work and to present our perspective concerning the problem areas that served to make the field so fascinating. However, this article does not, and is not intended to, present a balanced general historical review of the field. The research described would not have been possible without the active participation of many graduate students. Jerry Gold, who was a member of our group, first as a graduate student and then as a faculty colleague from 1967 until early retirement for health reasons in 1982, and Wayne McDaniel, who started as a graduate student in 1978 and continues to collaborate as a faculty member, played long-term key roles in our program.

Selection of Our Niche

There are many different and important aspects to ventricular defibrillation. No single group can reasonably hope to have the expertise to tackle all of them simultaneously. Very early in our work, we decided to focus most of our attention upon trying to relate the level of success in achieving defibrillation to the parameters of the electrical waveform utilized. We did this primarily because our group had the preexisting expertise to design and fabricate electronic circuitry to supply any desired waveform at any needed level. In addition, we had the background to interpret electrocardiographic data and to correctly and unequivocally monitor and/or calculate and interpret the significance of such variables as current, voltage, power, resistance, and duration together with a clear appreciation of the statistical nature of the defibrillation process and the need for enough experimental data to reach credible conclusions.

In a sense, our goal was not to discover the basic mechanisms of ventricular fibrillation and defibrillation on either a cellular or whole organ basis, but rather to generate an extensive database that would allow other investigators to check the validity of their hypotheses concerning mechanisms and to provide the kind of operational infor-

mation that would make possible the design of improved defibrillators for clinical use.

Our Research Defibrillators

Except for work with totally implanted systems, nearly all of the studies reviewed in this article were conducted with one or more of the four defibrillation systems described in this section. All of the systems were used over time intervals of many years and technically updated during their active life. Updated versions of two of the systems are still used in our continuing studies.

Linear Amplifier Based Defibrillator

Our first special research defibrillator was designed and constructed during the 1962–1963 era.[1,2] Based upon a 24,000/6,000 watt (W) linear amplifier whose abbreviated circuit diagram is sketched in Figure 1, the defibrillator was able to deliver almost any desired uniphasic waveform at levels up to 20 A and any biphasic waveform at levels up to 10 A. Initially designed for transthoracic work in medium sized (20–34 kg) dogs, the unit had provisions for the convenient delivery of a shock to induce fibrillation and a back-up shock, if needed, as well as for the delivery of the waveform being evaluated.

Thanks to the banks of beam-power tubes that were used, this unit inherently functioned as nearly a current-source amplifier: a fact that has important implications for its use in defibrillation research. Several years after its initial fabrication, this defibrillator circuit was updated by the addition of a simple current type negative feedback circuit; resulting in improved linearity and improvement in the precision of the current-source feature. Except for the capacitor banks that are housed in a large cart behind the apparatus, our linear amplifier defibrillator is contained in the center and left-hand relay racks shown in Figure 2. An updated version of the cart containing the capacitor banks is shown in Figure 3.

Uniphasic Hydrogen Thyratron Defibrillator

In order to remove the peak current limitation of 20 A imposed by our first research defibrillator, we next designed and built a defibrillator that used

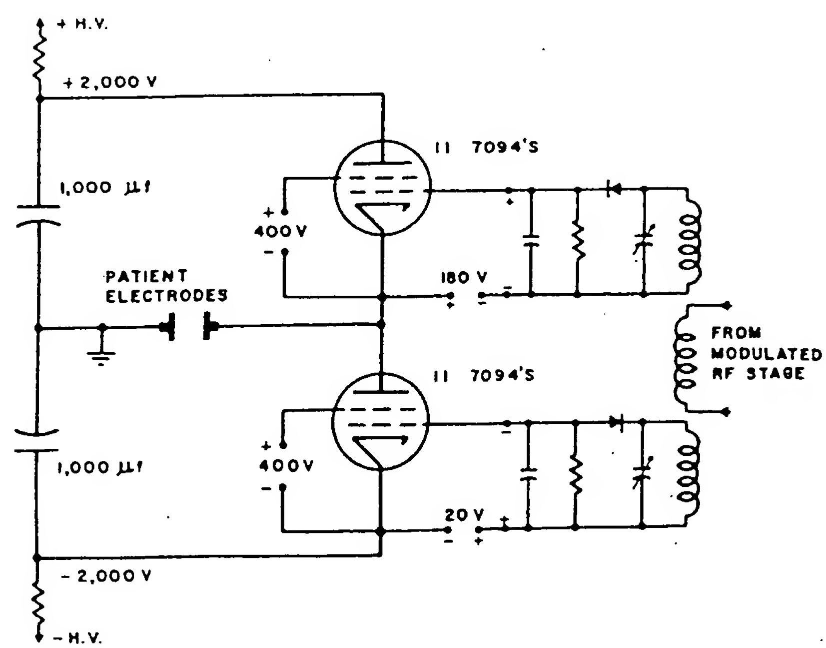

Figure 1. *High power stage of linear amplifier defibrillator. (Reproduced with permission.[1])*

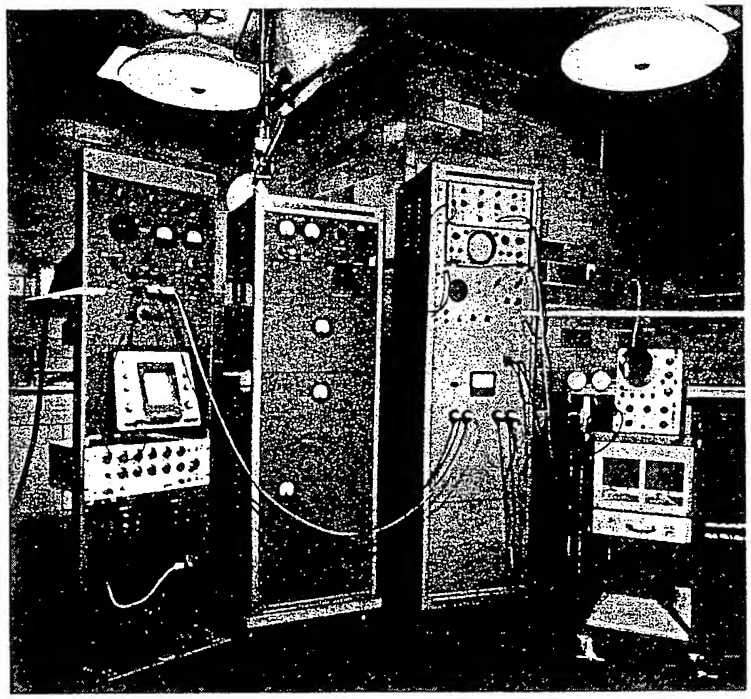

Figure 2. *Linear amplifier and hydrogen thyratron defibrillators configured so either may deliver shock. (Reproduced with permission.[3] © 1966 IEEE.)*

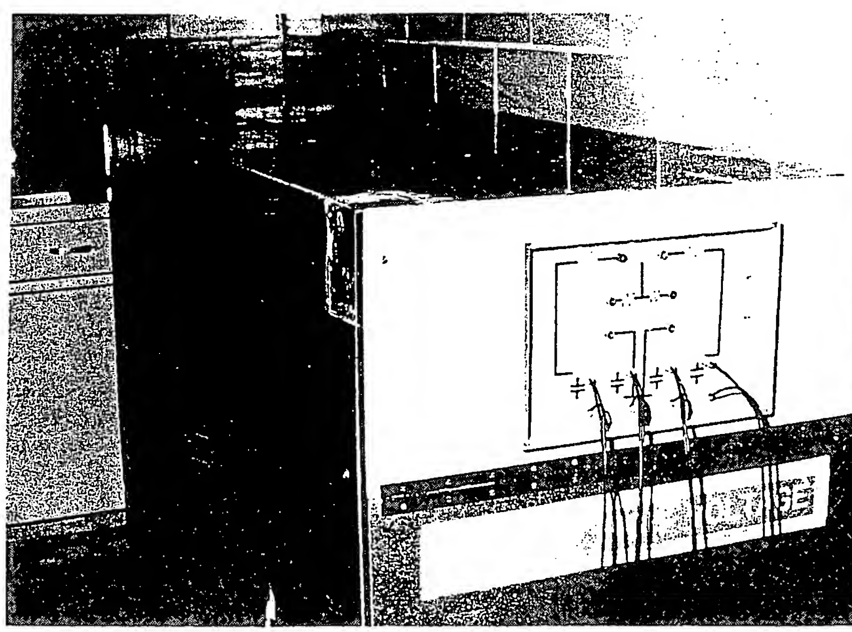

Figure 3. *Cart containing capacitor bank initially used with linear amplifier defibrillator.*

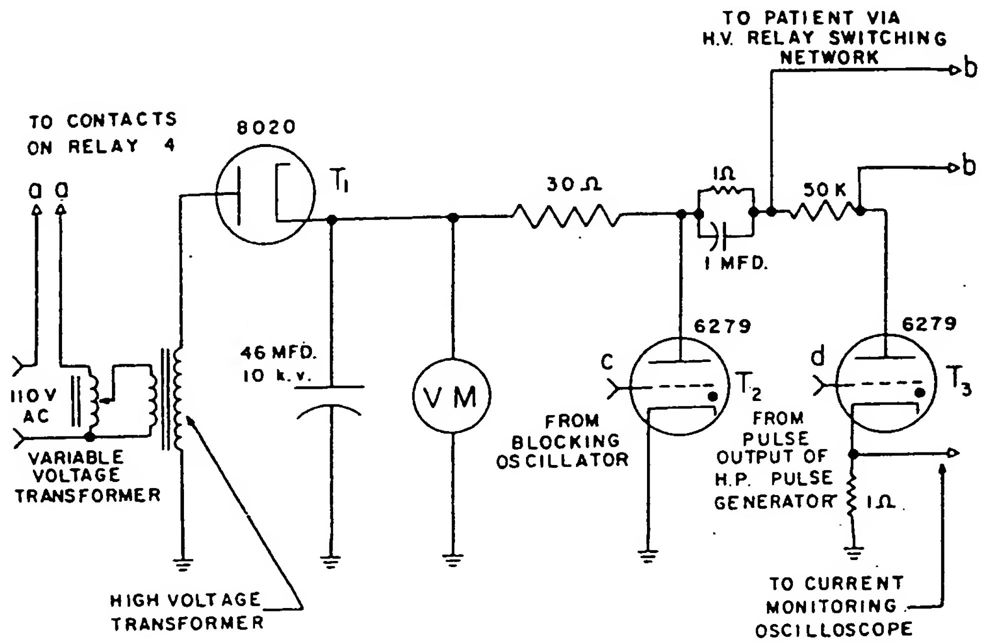

Figure 4. *High power portion of hydrogen thyratron defibrillator. (Reproduced with permission.[3] © 1966 IEEE.)*

hydrogen thyratron as electronic switches to initiate and terminate the discharge of a capacitor bank through the subject. Described in considerable detail in a 1966 article,[3] the unit whose circuit diagram is sketched in abbreviated form in Figure 4, was initially designed to furnish short, uniphasic, rectangular wave shocks at levels up to 100 A (600,000 W into a 60 Ω load) for transthoracic studies in medium sized dogs. Simple updating (provisions for selected resistance values to be added in series with the subject) greatly extended the capabilities of the apparatus to permit the generation of a wide variety of trapezoidal, truncated exponential, and untruncated exponential waveforms.

Lacking provisions for either inducing fibrillation or for supplying a back-up shock, this unit was intended to be used in conjunction with our linear amplifier defibrillator. Housed in the tall right-hand relay rack in the photo in Figure 2, the hydrogen thyratron defibrillator is shown interconnected with our first research defibrillator to allow the operator to easily route the desired defibrillator to a single pair of chest electrodes.

Unlike our linear amplifier, this hydrogen thyratron defibrillator and the two newer defibrillators to be described subsequently do not function as current-source generators. Consequently, the waveforms of current may vary with changes in electrode-to-electrode resistance unless appropriate adjustments are made by the operator during the course of an experimental fibrillation defibrillation session.

Multielectrode Time Sequential Defibrillator

While the two defibrillators described above were used quite successfully in an intensive screening program of candidate implanted electrode systems prior to our development of the completely implantable defibrillator, it was evident that it would be desirable to have a laboratory defibrillator with ratings appropriate to the internal defibrillation problem, having several pulse generators whose individual waveform parameters and pulse separations could be operator selected, and whose generators could be connected either to a pair of or to multiple electrodes in various configurations.

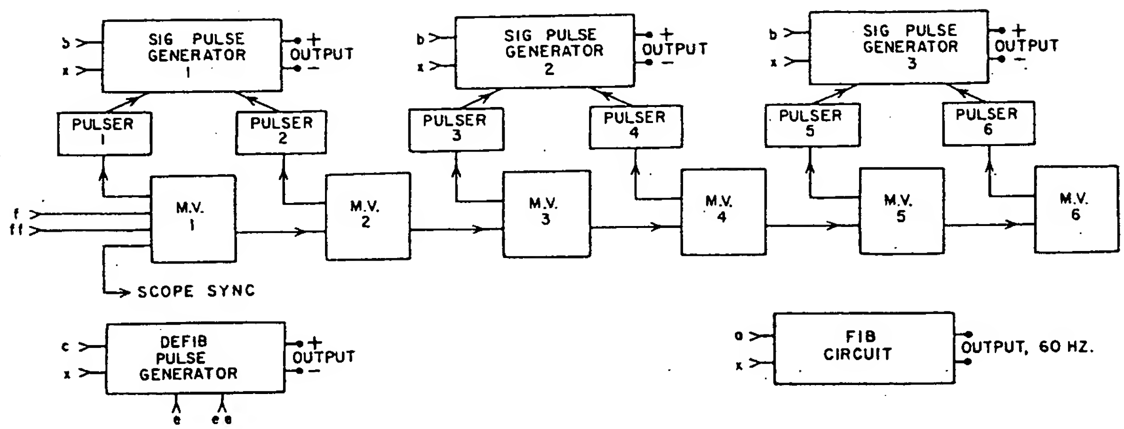

Figure 5. *Block diagram of core portion of multielectrode time sequential defibrillator. (Reproduced with permission.[4])*

A block diagram of the core portion of such a defibrillator, designed and fabricated in 1971 and described in detail in a 1972 article,[4] is sketched in Figure 5. The three signal pulse generators shown in the upper part of the sketch are identical: each uses a capacitor bank; a hydrogen thyratron for initiating the discharge; two silicon controlled rectifiers in series for terminating the discharge; and can supply uniphasic rectangular, truncated exponential, and untruncated exponential pulses with peak currents in excess of 20 A into a 50 Ω load and in excess of 10 A into a 100 Ω load.

The first five multivibrators in the chain below the signal pulse generators serve to provide both pulse duration and pulse separation, which are continuously adjustable from 100 μsec to 1 second. Since the outputs of the three pulse generators are completely isolated from each other and from ground, they can be patched to yield a large number of configurations at the four output terminals of the defibrillator yielding, for example: (1) a string of three pulses of the same polarity into a single electrode pair, (2) a string of three pulses of mixed polarity into a single pair, (3) one pulse into one electrode pair and another pulse into a second electrode pair (third generator unused), or (4) sequential pulses between each of three electrodes and a common fourth electrode. Shocks for inducing fibrillation and for back-up are provided by the generator blocks shown in the lower portion of the sketch. A front panel switch provides operator selection of fibrillation, test, or back-up shock.

As presently updated, each of the three signal pulse generators contains an internal capacitor bank operationally rated at 338 microfarads (μF) at 1200 V (243 joules [J] stored energy) with provisions for patching the banks that are contained in the cart of Figure 3 to yield a nominal operational stored energy rating of 603 J per generator. When the external capacitors are utilized, this defibrillator is also quite useful in transthoracic studies in medium sized dogs.

Although initially intended primarily for studies involving sequential shocks over multiple pathways, we actually used this apparatus in a series of other studies. Thus, credit goes to Geddes' group at Purdue for first studying the sequential shock-multipathway modality more than a decade later (Patent No. 4,548,203; Electrical system and method for implantable defibrillators, October 22, 1985).

Multifaceted Ultrahigh Energy Defibrillator

Initially motivated by an article by Tacker et al.,[5] which suggested that failure to defibrillate large patients might be due to output limitations on the available commercial defibrillators, the original version of this research defibrillator was designed and fabricated in 1975 to deliver uniphasic rectangular, truncated exponential, and untruncated exponential waveforms at current, voltage, power, and energy levels that one might anticipate would appreciably exceed the requirements

for transthoracic studies in 100-kg experimental subjects.

Described in detail in a 1976 article,[6] the initial version used three signal generators. The first furnished a 60-Hz signal of adjustable duration and amplitude for inducing fibrillation, the second source used an 18,000-J capacitor bank that could be patched to operate at up to 800, 1600, or 2400 V, and the third source used another 18,000-J capacitor bank that could be patched to operate at up to 5000, 10,000, or 15,000 V. Silicon controlled rectifiers were used as electronic switches for initiating and terminating the capacitor bank discharge in the second source: large hydrogen thyratrons were used for the same functions in the third source. By using the second source when longer duration, lower current pulses were required and the third source for shorter duration, higher current pulses, the apparatus could deliver an extraordinarily large range of waveforms.

The first system was housed in a two-bay relay rack, two large carts for the 18,000-J capacitors, and a box that contained a large automated transmitting type "antenna relay" for disconnecting the monitoring electrodes from the oscilloscope during the capacitor charge and shock delivery procedures.

The first major update in this defibrillator was undertaken in 1979–1980 following a hallway discussion at the Third Purdue Conference on Cardiac Defibrillation and Cardiopulmonary Resuscitation (1979) between Janice Jones, then at Case-Western Reserve, and Jerry Gold concerning possible advantages of biphasic over uniphasic waveforms in achieving defibrillation, a review of our own 1964 biphasic study in dogs,[2] and a study concerning underdamped sinusoids by Negovsky et al.[7] We incorporated a reverse current pulse generator into our then existing uniphasic defibrillator to yield a unit with biphasic capabilities. The new generator used an 18,000-J capacitor bank that could be patched for operation at up to 2,500, 5,000, or 10,000 V, a 16-unit string of silicon controlled rectifiers for initiating the capacitor discharge through the subject, and an 8-unit string of silicon controlled rectifiers for terminating the discharge. Designed to optimally and symmetrically interface with our existing lower voltage generator when it and the new generator were operated in their 2400/2500-V configuration and with our higher voltage generator when it and the new generator were operated in their 5000-V configuration, the new apparatus gave us biphasic rectangular, truncated exponential, and untruncated exponential capabilities based upon a stored energy level of 36,000 J.

Photos of the biphasic version of our ultrahigh energy defibrillator, now housed in a three-bay relay rack, are shown in Figures 6 and 7 and its three 18,000-J capacitor banks are shown in Figure 8. A unified description of this version of the defibrillator is provided in a 1982 article.[8]

The second major update in our ultrahigh energy defibrillator, carried out in 1985 and described in a short article in 1986,[9] involved providing triphasic waveform capabilities. Initially intended to be used primarily in the study of the transthoracic defibrillation of 100-kg calves, this modification, like the one before it, was an outgrowth of discussions with Janice Jones re the implications of some of her work involving cell cultures. While appreciably more limited in some of

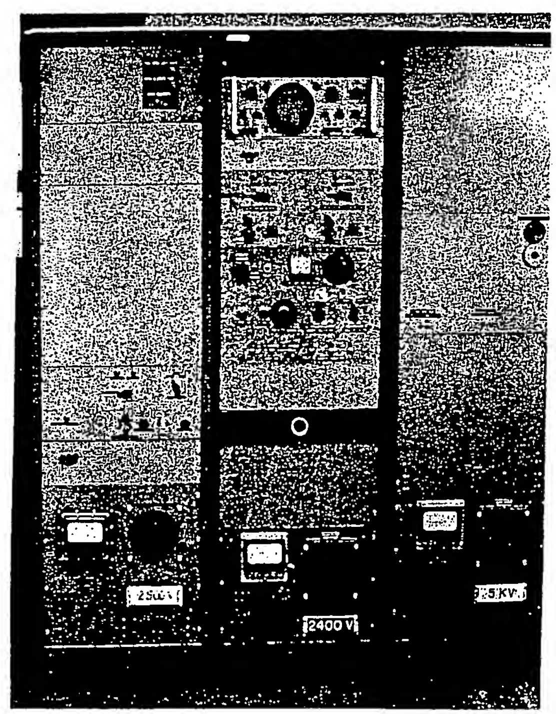

Figure 6. *Front view of multifaceted ultrahigh energy defibrillator.*

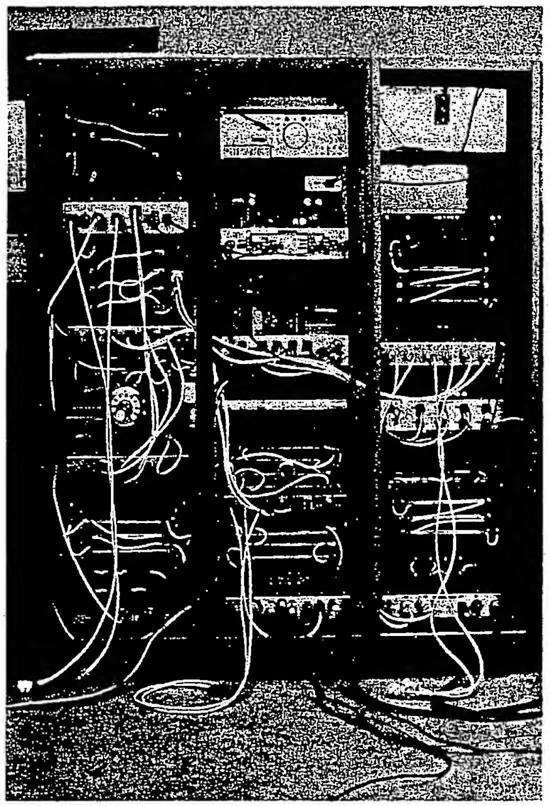

Figure 7. *Rear view of multifaceted ultrahigh energy defibrillator.*

its ratings when configured in the triphasic mode than it is in either the uniphasic or biphasic modes, the defibrillator is still capable of delivering high quality triphasic rectangular wave shocks of up to 100 A as well as triphasic truncated and untruncated exponentials into our calf model. Physically, the apparatus still looks much the same as shown in Figures 6, 7, and 8.

In addition to its primary function involving transthoracic defibrillation studies in large animals, the defibrillator also has been used extensively in transthoracic studies in dogs and for studies involving implanted electrode systems in small and large animals. Furthermore, temporary modifications have allowed us to use the defibrillator to compare the effectiveness of one-cycle quasisinusoidal waveforms with critically damped sinusoids in the transthoracic defibrillation of 100-kg calves as well as to simulate "single capacitor" type waveforms for implantable electrode system studies.

Experimental Philosophy and Protocol

In designing the protocol for our experimental studies, we have paid particular attention to maintaining the kind of consistent procedures and routines that permit easy interpretation of results and the meaningful comparison of data from studies conducted at different times.

Probably the single most significant feature of nearly all of our studies has been the use of the current versus time waveform as an independent variable. Depending upon the broad category of waveforms being studied, this may involve denoting, for example, such parameters as duration, amplitude, and generic shape. Our reason for selecting current rather than voltage as the independent variable was that by so doing the time and spatial distribution of the current density vector within the heart is made substantially independent of electrode—skin (electrode—internal tissue) interface resistance changes for a given animal having given positions of the electrodes. Thus, changes in observed efficacy of defibrillation reflect actual waveform changes in the variable rather than a mix of waveform and interface influenced changes. Parenthetically, experimental artifacts such as, for example, ECG paste bridges between skin electrodes that would tend to favor voltage over current sources, are considered by us to be easier to avoid than are the interface resistance shift problems.

Of our four research defibrillators, only the linear amplifier unit automatically provided current-source waveforms; the other three require episode-by-episode tracking and operator intervention during the course of a session.

Most of our studies used either dogs or calves. Except when questions regarding the influence of animal weight were specifically under investigation, dog weights were almost always in the 20- to 34-kg range, calf weights were 90–110 kg, fibrillation was induced with a low current 60-Hz shock, the time interval between the induction of fibrillation and an attempt to defibrillate with the shock being evaluated was 30 seconds, back-up shocks of known high efficacy were used to salvage ani-

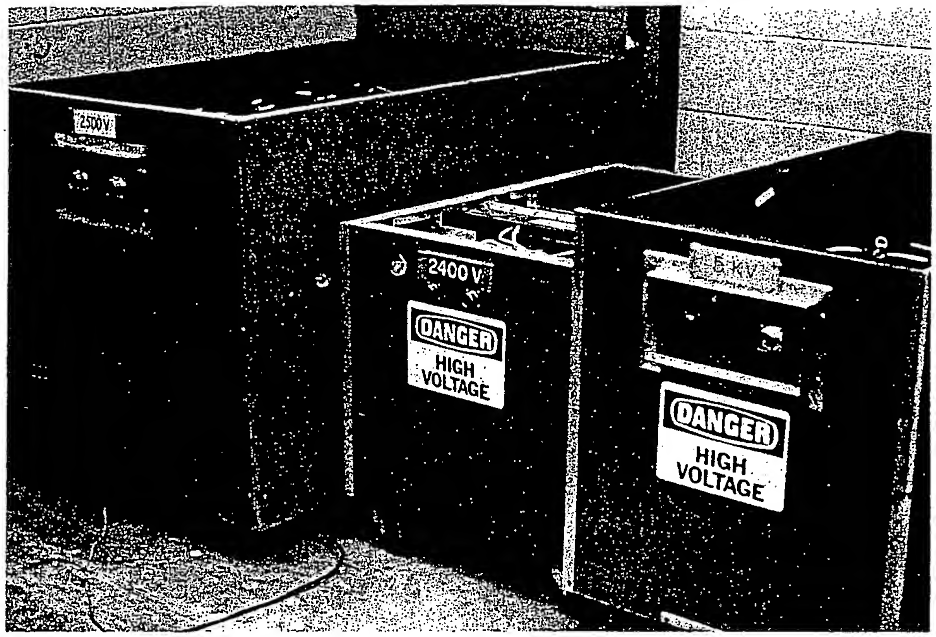

Figure 8. *Carts containing three 18,000-J capacitor banks. Capacitors in banks may be patched to yield a variety of voltage ratings.*

mals in case of failure to defibrillate with the shock being evaluated, transthoracic dog electrodes were 9.0 cm in diameter, and transthoracic calf electrodes were 13.0 cm in diameter. Dogs were anesthetized with pentobarbital sodium injected intravenously at 27.5 mg/kg body weight (with more as needed) and calves were maintained with methoxyflurane in 50% N_2O and 50% O_2,following low dose guidelines with automatic assisted ventilation.

In nearly all of our transthoracic studies in dogs and calves, at least six animals were used to evaluate the effectiveness of defibrillation and (usually) the nature of the postdefibrillation electrocardiogram for each specific experimental condition considered. With at least 3 minutes between the start of successive episodes, each animal was carried through a maximum of 20 fibrillation-defibrillation episodes involving the waveform being evaluated with additional animals being used, if required, to obtain a total of 120 episodes per waveform evaluated. With at least 1 day intervening between successive sessions with a given animal, the animals were then ordinarily reused in the evaluation of other waveforms. By letting one or two parameters of a category of waveforms take on a succession of values, we were able to generate curves and families of curves of percent successful defibrillation versus the parameters of interest. Since many of these transthoracic studies involved several dozen explicit waveforms and each waveform required 120 episodes, the individual studies often involved several thousand fibrillation-defibrillation episodes.

Our extensive work with implanted electrode systems has followed the same general philosophy as that with transthoracic systems, with an emphasis upon generating curves of percent success versus some parameter of the shock waveform. However, work with these electrode systems has often involved acute studies, up to 60 fibrillation-defibrillation episodes per session, interlacing of waveforms tested, and the generation of a less extensive database.

While we view our overall defibrillation research effort as possessing a high level of integration, in the various Results and Discussion sections that follow, we have, somewhat arbitrarily,

subdivided our studies on the basis of various combinations of such factors as species, electrode systems, generic waveforms, and the methods of interpreting results. Generally appearing in approximate chronological order, some of our studies appear out of sequence so as to better fit into the subject oriented section format mentioned immediately above.

Finally, the Result and Discussion sections below are intended to cover only those features of our overall effort that were controversial or of special interest at the time the research was carried out, have played a continuing role in our growing understanding of defibrillation, or appear to suggest new avenues of research: the material does not constitute an all inclusive account of our work.

Transthoracic Ventricular Defibrillation in the Dog

Our first extensive study (1960–1961 era) related success in achieving defibrillation and survival to the duration of unassisted ventricular fibrillation before closed chest massage[10] was initiated (followed by transthoracic shock) and to the emergency type drug used. This study was unique for us in that it was the only one to use massage as an integral part of the evaluation protocol and the only one to use the then widely used 60-Hz AC defibrillator.[11,12] Our finding with intracardiac injection of epinephrine is that one can achieve a relatively high defibrillation and survival rate in the dog after as much as 10 minutes unassisted fibrillation.[13]

Before leaving the only explicit mention of the 60-Hz sinusoidal AC defibrillator in this article, it should be emphasized that its rapid decline in clinical usage during the 1960s was not solely because of presumed superiority of other waveforms. In fact, as we shall show later, there now is good reason to believe that if the total duration specifications of 0.1 or 0.25 seconds are relaxed, some AC waveforms can be quite effective. A real advantage of the defibrillators that came into use in the 1960s was that they removed energy from the source over a period of seconds (rather than in real time as it is delivered to the patient) and thus avoided the multiple problems associated with enormous temporary overloads of electrical systems (with blown fuses, open circuit breakers, malfunctioning timers) or the need for heavy and complicated battery-inverter units for portable operation.

The core portion of our transthoracic work in dogs published during the 1964–1971 period is contained in six studies and involved a total of 34,560 fibrillation-defibrillation episodes. Briefly, the subjects investigated were: (1) 5-, 10-, and 20-A uniphasic, biphasic, and multiphasic rectangular waveforms;[2] (2) uniphasic triangular and trapezoidal waveforms;[14] (3) 20–100-A uniphasic rectangular waveforms;[15] (4) arrhythmias associated with 10–100-A uniphasic rectangular waveforms;[16] (5) uniphasic double rectangular pulses;[17] and (6) uniphasic truncated and untruncated exponential waveforms having initial currents in the 10- to 100-A range.[18]

Our data from the studies involving 5-, 10-, and 20-A uniphasic rectangular wave shocks from a 1964 article in Circulation Research[2] are sketched in the graph of Figure 9. Because these waveforms are so simple and so easy to describe, several features of the resultant family of curves deserve comment. First, the 10-A and 20-A curves peak at essentially the 100% success level. Since the curves peak at about 16- and 4-msec duration, respectively, and delivered energy in joules is given by the product of current in amperes^2, pulse duration in seconds, and chest resistance (about 60 Ω), both waveforms require about 96 J for peak percent success. Second, the 5-A curve never reaches the vicinity of 100% success. Shocks with too small current amplitudes simply are not effective, irrespective of energy content (as we shall find later, the same comment also applies to shocks of excessive current amplitude). And finally, after reaching their respective peaks, each of the three curves of Figure 9 yields decreased effectiveness with increasing pulse width. In the graph of Figure 10 are sketched corresponding curves of percent success versus pulse duration for 5-A uniphasic and "quasibiphasic" rectangular wave shocks.[2] The apparent broadening of the response curve of the quasibiphasic over the corresponding uniphasic waveform as shown here (another graph in the original article showed somewhat similar results at 10 A), was one of the motivating factors for us to reconsider biphasic waveform defibrillation some 20 years later! Parenthetically, in this particular study the quasibi-

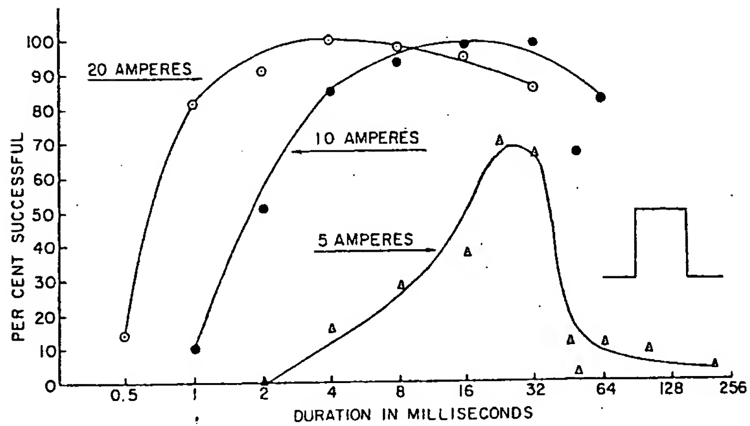

Figure 9. *Relation between percent successful defibrillation and duration of transthoracic 5, 10, and 20 ampere uniphasic rectangular wave shocks in dogs. (Reproduced with permission from the American Heart Association, Inc.[2])*

phasic waveform was generated by closing and opening an unsynchronized electronic switch to connect and disconnect a continuous square-wave source to the defibrillator amplifier input for a period equal in duration to just one cycle, thus sometimes yielding a biphasic and sometimes an asymmetrical triphasic waveform.

The results of our uniphasic triangular and trapezoidal wave studies, carried out largely by Glenn Rahmoeller[14] and published in 1966, are shown and plotted in terms of duration of pulse in Figure 11, and in terms of delivered energy (60 Ω chest resistance assumed) in Figure 12. To permit convenient comparison, the data plotted in Figure 9 is also replotted, in terms of energy, as the bottom graph of Figure 12.

The data shown in Figures 11 and 12 have played a key role in our operational understanding of the defibrillation process as well as serving as the experimental rationale for early commercial trapezoidal wave transthoracic defibrillators (for example, those manufactured by Medical Re-

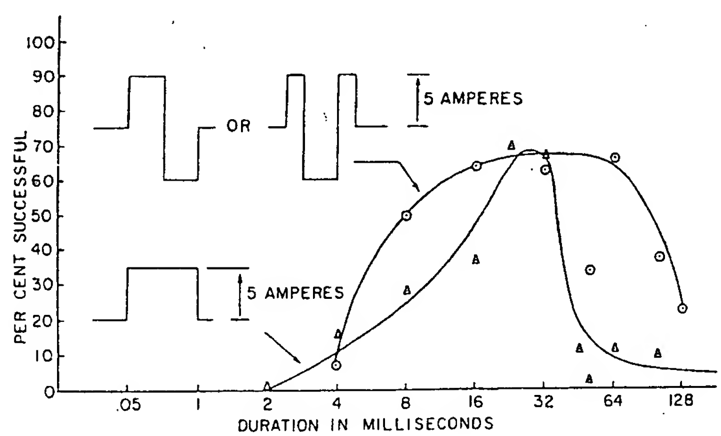

Figure 10. *Relation between percent successful defibrillation and duration of transthoracic 5 ampere uniphasic and 5 ampere quasibiphasic shocks in dogs. (Reproduced with permission from the American Heart Association, Inc.[2])*

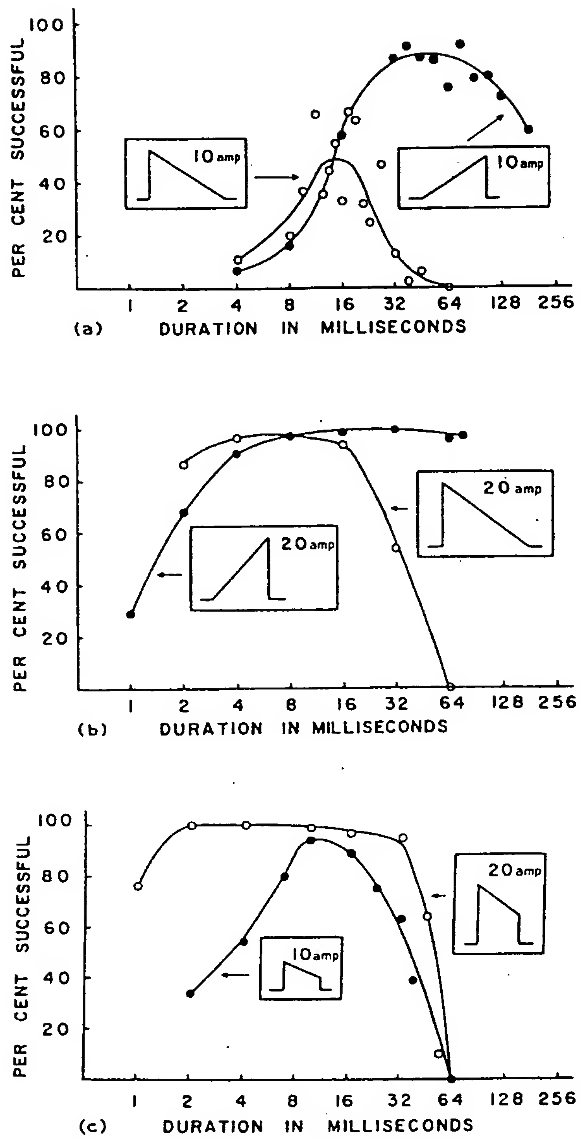

Figure 11. *Relation between percent successful defibrillation and duration of transthoracic shocks in dogs; 10 amp (amp) triangular (a); 20 amp triangular (b), and trapezoidal (c). (Reproduced with permission from the American Heart Association, Inc.[14])*

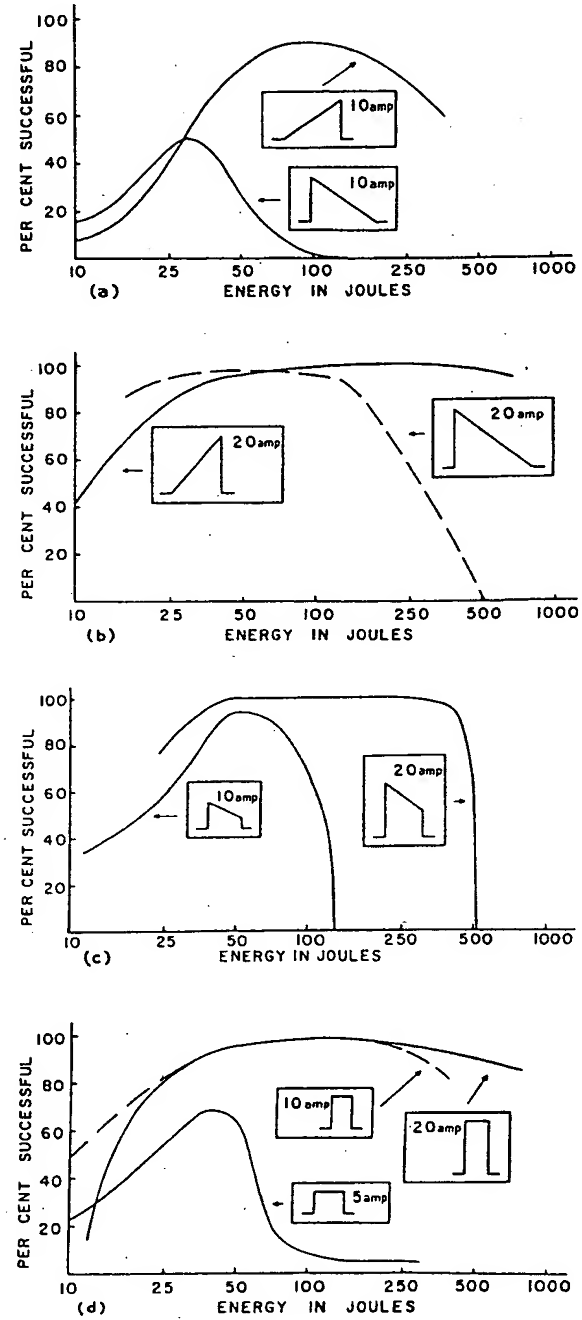

Figure 12. *Relation between percent successful defibrillation and energy content of transthoracic shocks in dogs. A 10 ampere (amp) triangular (a), 20 amp triangular (b), trapezoidal (c), and rectangular (d). (Reproduced with permission from the American Heart Association, Inc.[14])*

search Laboratories [Buffalo Grove, IL, USA] and Health Tech [Omaha, NE, USA]) and for the trapezoidal waveform used in the first generation of experimental and clinical implantable defibrillators.[19,20] From the data in Figures 11(a) and 12(a)

it is unequivocally evident that for the longer and higher energy 10-A shocks, there is a tremendous spread in percent successful defibrillation between the ascending ramp triangular and descending ramp triangular waveforms. The same phenomenon is illustrated with even greater clarity in Figures 11(b) and 12(b) for 20-A triangular waveforms. In Figures 11(c) and 12(c), are shown plots of percent success versus duration and energy for 10-A and 20-A trapezoidal waveforms generated by simply truncating at the specified duration descending ramp triangular waveforms that would otherwise have decreased to zero at 64 msec. Again, one observes dramatic results; by simply deleting an appropriate portion of the "tail" of a descending ramp triangular waveform, its percent success in achieving ventricular defibrillation jumps from 0% to 100% or nearly 100%. In comparing data in Figures 12(b), 12(c), and 12(d), it is evident that over a wide energy range, ascending ramp triangular and trapezoidal waveforms yield the same near 100% success rate as do uniphasic rectangular wave shocks.

The observation outlined in the previous paragraph led us to introduce the operational concept of "refibrillation." That is, we hypothesized that in uniphasic waveforms with long, low amplitude tails, the leading portion of the waveform may well defibrillate the heart only to have it refibrillated by the low amplitude lagging portion of the waveform. As we soon shall see, our studies of the arrhythmias associated with waveform parameters[16,18] tend to strongly support this simple operational concept.

Our study of 20- to 100-A uniphasic rectangular waveforms that was published in 1967[15] showed that for any given energy content, the percent success tends to decrease as the current level appreciably exceeds 20 A. Just as shocks with too low a current level are less successful, so too are shocks delivered at excessive current levels.

At about the time this particular study was being conducted, there was considerable controversy as to whether extremely rapid jumps in current adversely influenced the success rate of shocks intended to defibrillate. If so, the argument went, this might explain why the widely used Lown type waveform with its relatively slow rise in current seemed to perform so much better than waveforms generated using only a capacitor. In a supplementary study designed to resolve the matter, we interlaced fibrillation-defibrillation episodes involving 20-A–1-msec rectangular wave shocks from our linear amplifier defibrillator[1,2] with episodes from our uniphasic hydrogen thyratron unit[3] (the linear amplifier had average rise and fall transit times in the order of 300 μsec, the hydrogen thyratron unit, in the order of 3 μsec). The results of this 240 episode supplementary study,[15] which are shown in Figure 13, clearly fail to demonstrate any difference in effectiveness between the two waveforms. We concluded that whatever the reason for the relatively ineffectiveness of the straight capacitor discharge in achieving defibrillation, it was not because of the fast initial current jump per se.

In a study published in 1968,[16] we reported how a variety of postdefibrillation arrhythmias were related to the current amplitude and energy content of 10- to 100-A uniphasic rectangular wave shocks. Figure 14 shows the relationship between percent of successful shocks having any arrhythmia and energy content for five current lev-

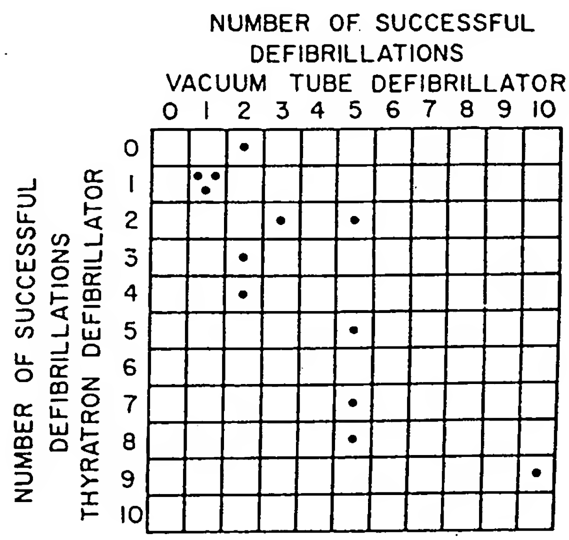

Figure 13. *Comparison of results of 20 A, 1-msec transthoracic shocks in dogs delivered with thyratron and vacuum tube (linear amplifier) defibrillators. Each dot represents the results of a series of ten episodes from the thyratron defibrillator interlaced with ten episodes from the linear amplifier defibrillator. (Reproduced with permission.[15])*

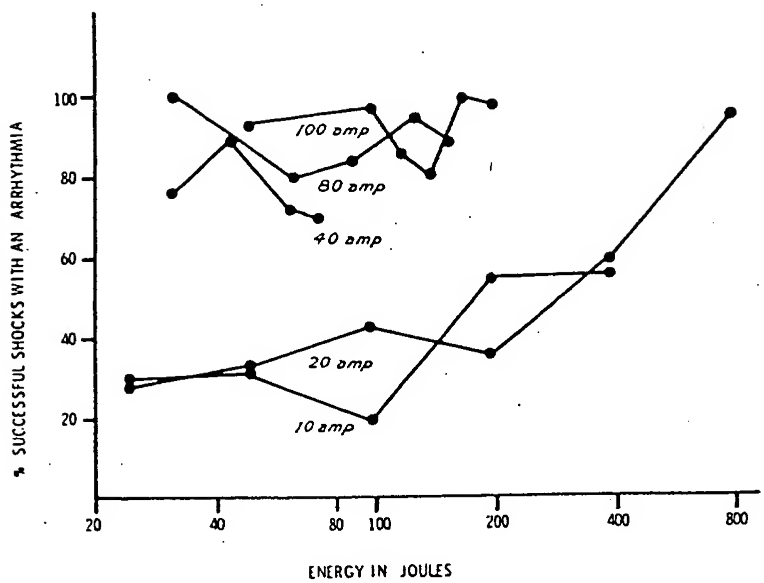

Figure 14. *Relation between percent of successful shocks accompanied by any type of postdefibrillation arrhythmia and energy content of uniphasic rectangular wave shocks in transthoracic defibrillation in dogs. (Reproduced with permission from the American Heart Association, Inc.[16])*

els. Similar trends are observed if the average number of kinds of arrhythmias is plotted along the vertical axis. The results indicate: (1) a high level of postdefibrillation arrhythmia activity is present when either excessive current or excessive energy is used, and (2) increasingly higher levels of arrhythmia activity are eventually accompanied by rather slowly decreasing percent successful defibrillation levels. Operationally, we interpret the downturn in percent successful defibrillation as being a reflection of a generalized temporary "damage" to the conduction system and quite different than the rapid drop in percent successful defibrillation observed with the refibrillation phenomenon associated with the low amplitude tails of some waveforms.

Over the years there has been recurrent interest among investigators in the possibility of reducing the total energy required for defibrillation by using a series of two or more shocks in time sequence. We have conducted two extensive studies: the first, published in 1970[17] and described in this paragraph, involved the transthoracic defibrillation of dogs with uniphasic rectangular double pulses separated by 70–130 msec; and the second, entirely different in focus, involved 100-kg calves with shock separations of 15 seconds. Motivated primarily by reports from Kugelberg,[21,22] which suggested that 20-msec rectangular double pulses separated by 100 msec required much less total energy to defibrillate perfused hearts, we conducted a 4560 episode transthoracic double pulse study and compared our results to those of our earlier single uniphasic rectangular pulse studies.[2] We were unable to demonstrate the superiority of double pulse shocks over appropriate single pulse shocks and, in fact, only with shorter duration–higher amplitude pulses did the double pulse arrangement begin to approach the single pulse in defibrillation efficacy.

Our final transthoracic study in dogs, published in 1971[18] was extensive, involving 10,560 fibrillation-defibrillation episodes and allowing us to generate families of curves involving untruncated and truncated exponential waveforms varying from 10 through 100-A initial current, 60 through 180 J "stored" energy, and truncation levels of 0 through 15 A. The results confirmed our expectations from earlier studies[2,14,15] and clearly showed the general efficacy of uniphasic trun-

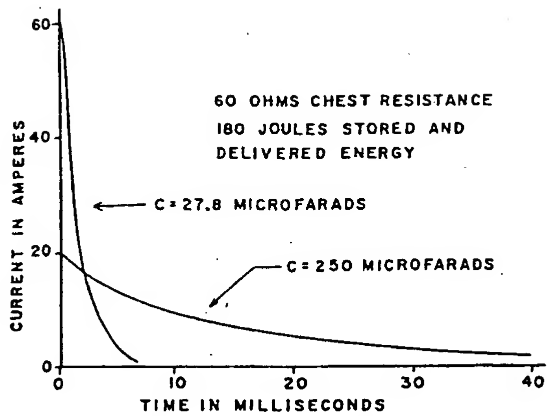

Figure 15. *Current versus time waveforms that illustrate the reason for the dilemma in trying to defibrillate with untruncated capacitor discharges.*

cated exponential waveforms. Furthermore, they made evident the operational dilemma with trying to defibrillate with untruncated exponential waveforms. At any given stored energy level, one can charge a large capacitance (as measured, for example, in microfarads) to a low voltage or a small capacitance to a high voltage. The first choice yields low initial current with a slowly decaying tail together with the frank refibrillation phenomenon noted with the descending ramp triangular waveform.[14] The second choice yields a high initial current and rapid decay. It gives less than optimal results because of the high initial current (as in our uniphasic rectangular waveform study).[15] Unfortunately, there appears to be no broad middle ground where both adverse influences are minimal or absent; thus, the need for truncation or other type of waveform shaping. The dilemma is illustrated, with parameters relevant to the transthoracic defibrillation of a dog, in the current versus time sketches of Figure 15.

The Automatic Implantable Defibrillator

Early Phase

The story of the early phase of the development of the automatic implantable defibrillator is an intriguing one; made more so by the independence of conception and nearly simultaneous publication by Michel Mirowski's group and by our group. The legal aspects of the subject, a matter of extensive litigation by several companies, are not considered here. I shall concentrate upon the contributions made by our group and our perspective of the roles played by the two groups.

In one sense, it started for us on a sidewalk as I waited for a shuttle bus to return me to my motel or hotel room following an afternoon session of the American Heart Association meeting in Dallas (November 13–16, 1969). As I waited, I reviewed possible projects for future work and among them was the automatic implantable defibrillator! Thinking about the problem, and based upon our background in transthoracic defibrillation, knowledge about waveform efficacy, and an appreciation of circuit design and component problems, it was almost immediately apparent that the automatic implantable defibrillator was a doable project. I decided to go home and do it.

Our laboratory databook indicates we started the experimental portion of our work (in dogs) on the automatic implantable defibrillator (evaluation of candidate electrode systems) just after the completion of the day's work on our then ongoing transthoracic study on November 21 or just before the start of the day's work on our transthoracic study on November 22, 1969.

Having completed the design and fabrication of the system and carried out many additional animal studies, the first complete test of our automatic and completely implanted defibrillator was carried out in a 22-kg dog on January 16, 1970.[19] On that first day, the animal was fibrillated 13 times with the implanted system successfully reversing the fibrillatory process in all 13 episodes (in eight of the episodes defibrillation was achieved with the first shock, three episodes required the system to automatically cycle through two shocks, and two episodes required three shocks). The animal survived the study. At the end of the study, the following comment appears in our laboratory databook: "So far as I am aware, this represents the first time a completely implanted and automatic defibrillator has been successfully used. The results are conclusive and would seem to indicate that it should be possible to develop a unit for use in humans within the broad weight and volume requirements which might be applied."

Two months from conception to quite adequate performance in an experimental animal sounds like an incredibly rapid pace for any new electrophysiological device development project. But then, the effort was really based on a decade of prior defibrillation research and decades of experience in working with relevant electronic circuitry.

To appreciate the near simultaneous release of information about the automatic implantable defibrillator by Mirowski's group and by our group, consider the following chronology. Our first article entitled "Experimental ventricular defibrillation with an automatic and completely implanted system" was presented at the 16th annual meeting of the American Society for Artificial Internal Organs in Washington, D.C. on April 9, 1970 and published as a full length article in volume 16 of the Transactions American Society for Artificial Internal Organs.[19] An old notation in records indicate this volume was distributed in June 1970.

What was apparently the first article by Mirowski's group, entitled "Standby automatic defibrillator—An approach to prevention of sudden cardiac death," was received for publication on April 16, 1970 by the Archives of Internal Medicine and published in the July 1970 issue of the journal.[23]

While the two initial articles[19,23] emphasized the same goal related concept, they differed sharply in other respects; reflecting the different roles of the two groups in the period before initial publication. Most of these differences were briefly enumerated in two letters to the editor by myself (Journal of the American Medical Association, November 9, 1970; and Archives of Internal Medicine, February 1971).[24,25]

Succinctly, the differences in the initial articles were: (1) that Mirowski proposed an intracardiac catheter electrode in conjunction with one under the skin for delivering the shock, we used electrodes implanted between the pectoralis major muscle and the rib cage; (2) Mirowski detected fibrillation with a pressure transducer in the right ventricle, we used electrocardiographic signals for detection; (3) Mirowski used a simple high voltage capacitor to yield an untruncated defibrillatory shock, we truncated a lower voltage capacitor discharge to furnish a trapezoidal wave shock; (4) Mirowski's studies were carried out with large apparatus external to the body and, beyond reporting some successes and presenting electrocardiographic traces from two episodes, provided little experimental data, we presented detailed results in studies in three dogs containing completely implanted and totally automatic systems and encompassed a total of 73 successful fibrillation-automatic defibrillation episodes; and finally (5) while Mirowski discussed the need for such devices in somewhat general terms, we concentrated more on such detailed items as weight, longevity, and engineering problems that might be anticipated and improvements that might be considered in future developmental work.

Taken from our initial article,[19] a block diagram of the version of the defibrillator used in the first (and following) dogs is shown in Figure 16. The actual physical system, purposely arranged so each subunit corresponds to a block in Figure 16, and before being encapsulated for implantation, is shown in Figure 17. A slightly later version, in which the DC–DC converter, pulse generator, and fibrillation detector are combined into a single board is shown in Figure 18.

The source of funding for the development of the automatic implantable defibrillator has been the subject of some published comment. Although funding for both efforts has been attributable to personal participants,[26] at the time of the initial developmental work, our general cardiac research work was funded by a grant from the Missouri Heart Association, two grants from the National Heart and Lung Institute, and conducted during my tenure as an established investigator of the

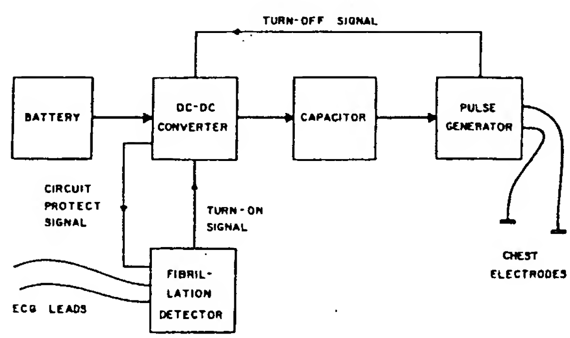

Figure 16. *Block diagram of our completely implantable automatic defibrillator. (Reproduced with permission.[19])*

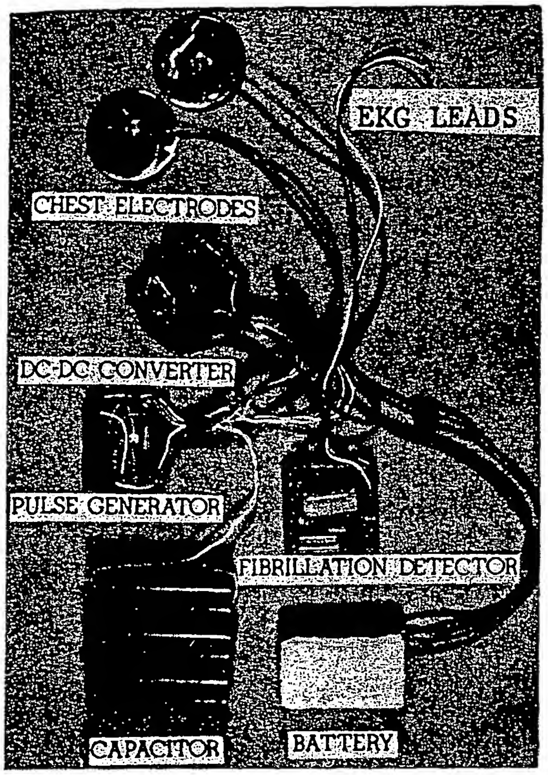

Figure 17. *A very early, completely implantable automatic defibrillation system (boards purposely arranged to correspond to block diagram shown in Fig. 16). (Reproduced with permission.[19])*

American Heart Association. While regulations required that inventions be reported, our request that a patent not be sought was honored and we were able to freely publish and discuss all aspects of the device and its circuitry.

Mirowski, on the other hand, did seek and obtain patents. While our laboratory group was primarily interested in continuing to study a variety of aspects of defibrillation and in developing and evaluating new waveforms, Mirowski, with admirable singleness of purpose, seemed determined to quickly steer the automatic implantable defibrillator through the pitfalls of both a part of the medical establishment and a part of corporate America to a viable role in preventing sudden cardiac death!

Apparently having been approached by Mirowski about the possibility of further developing and manufacturing an implantable defibrillator, Medtronic, Inc., with the presumed concurrence of Mirowski, contacted our group in late 1970 (or possibly early 1971) about undertaking a quick study of the feasibility of an intravascular catheter system utilizing one electrode positioned in the apex of the right ventricle and the other in the superior vena cava. Funded by and using catheters furnished by Medtronic, we started the animal study on February 3, 1971. Conducting first a pilot study involving various waveforms, we later carried out a systematic study using 18.5- and 37-J uniphasic truncated exponential shocks in dogs. Published first as a short article in October 1971[27] and then as a full length paper in 1973,[28] our results, although quite limited in scope, were generally favorable to the all catheter type system.

Despite encouraging research results, and presumably because of reservations about patient/physician acceptance of such a device, commercial development of the implantable defibrillator was not immediately initiated.

An editorial concerning the automatic implantable defibrillation work of our group and Mirowski's group by Bernhard Lown and Paul Axelrod,[29] which appeared in the October 1972 issue of Circulation, probably correctly reflected the views of many physicians at the time with its comment, " . . . In fact, the implanted defibrillator system represents an imperfect solution in search of a plausible and practical application." A refutation of the editorial in the form of a letter to the editor by Mirowski and colleagues appeared in the May 1973 issue of Circulation.[30]

Following the period of interaction with Medtronic, Mirowski, in his determination to see the automatic implanted defibrillator quickly become a clinical reality, worked with Medrad (later Intec Systems, and still later Cardiac Pacemakers, Inc.) and our group turned to a study of a variety of topics involving implanted and transthoracic systems. It was to be more than a decade before we again directly interacted when the University of Missouri, with Hugh Stephenson, Jr. as the principal investigator, became one of the fairly early centers in the premarketing clinical study of Mirowski's automatic implantable defibrillator.

Later Phase

In the 20 or so years since the initial round of excitement over the implantable defibrillator,

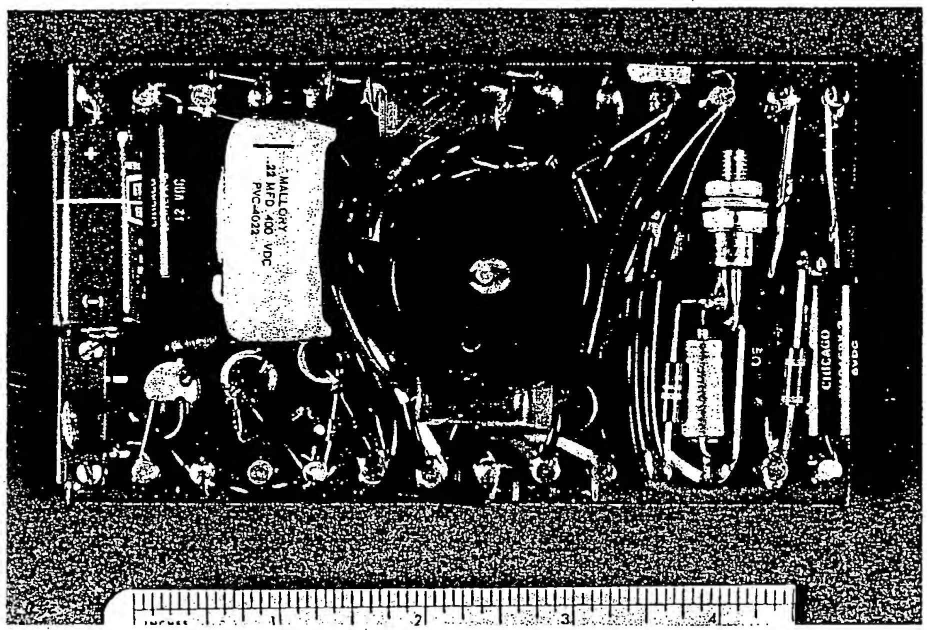

Figure 18. *Defibrillator circuit board in which fibrillation detector, DC—DC converter, and pulse generator are combined.*

most of our research has involved first demonstrating innovative new concepts on either a transthoracic basis or on an electrode system independent basis before undertaking detailed studies with implanted electrodes. Consequently, the most significant portion of this work will be summarized in succeeding sections of this article.

However, two somewhat unique studies will be surveyed in the present subsection. The first involves a definitive study of the relationship between catheter electrode geometry and effectiveness of ventricular defibrillation in dogs that appeared in the September 1973 issue of Cardiovascular Research,[31] and the second, reported in abstract form in 1987[32] and as a full length article in 1989,[33] pointed out the adverse effects of internal defibrillator patches on the efficacy of transthoracic defibrillation in calves.

A sketch of the electrode arrangement on the experimental catheter is shown in Figure 19. The three more distal sleeves are 6 mm in length and separated by 2 mm. The four more proximal are 20 mm in length and separated by 25 mm. All of the sleeves are 4.1 mm in diameter. The individual insulated leads from each sleeve pass through the lumen of the catheter where they can be interconnected as desired (or left floating). The catheter was inserted through an external jugular vein of 24- to 31-kg dogs and the tip positioned in the apex of the right ventricle. Sixty combinations of sleeve connections were studied in two series involving 720 fibrillation-defibrillation episodes each. The combinations and sequence in which they were evaluated in each dog is shown in Figure 20. The first series used uniphasic rectangular wave shocks having an amplitude of 6 A and a duration of 5 msec. The second series again used 6-A shocks, but the duration was varied from combination to combination to keep the delivered energy essentially invariant at 21 J.

In clearly delineating the geometrical conditions necessary for efficient defibrillation with a bielectrode catheter system, this innovative study yielded two important concepts with implications for clinical application: First, " . . . the position of the electrode within the right ventricle is critical. Failure to position the tip in the apex (as simulated in our study by the nonuse of sleeve A) or failure of the tip to remain in position can cause a definite decrease in system effectiveness or, alternatively,

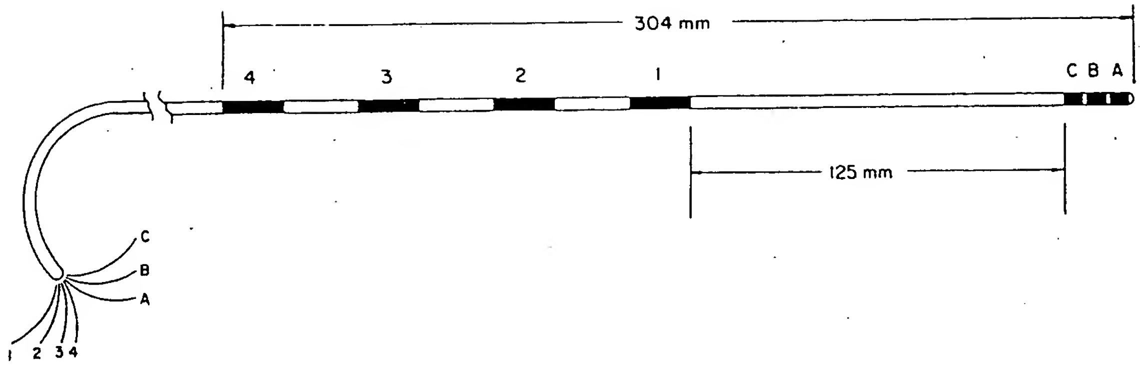

Figure 19. *Experimental defibrillation catheter. (Reproduced with permission.[31])*

in the need for greater energy to achieve a given level of effectiveness." Second, ". . . provided sufficient area is present, the position of the electrodes in the superior venous system is not particularly critical."[31]

Clinical applications of implantable defibrillators have often involved two large mesh patches sutured to the ventricles and covered by insulating material on the surface that is not in contact with the heart in order to minimize electric current streamlines (and wasted energy) in regions other than the heart. This system is often used when it is anticipated that smaller electrodes might fail to achieve defibrillation. These large electrodes are sometimes implanted at the time of other heart surgery without the defibrillator itself being implanted.

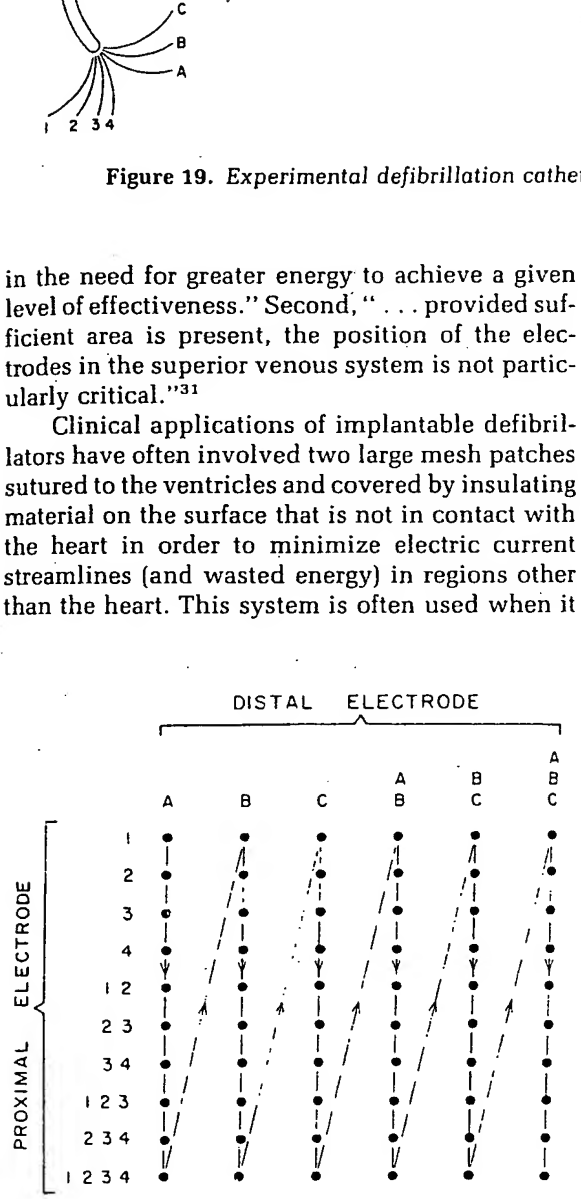

Figure 20. *Sequence in which 60 combinations of sleeves of catheter shown in Figure 19 were studied. (Reproduced with permission.[31])*

In the mid-1980s, clinical experience by the Cardiothoracic Surgery group at the University of Missouri suggested that the presence of such internal patches (model L67, Intec Systems [Cardiac Pacemakers, Inc., St. Paul, MN, USA]) hindered the ability to defibrillate on a transthoracic basis.

A cursory theoretical analysis indicated that a patch configuration such as this, in which a considerable portion of the surface area of the heart may be covered by the electrodes will, indeed, result in major changes in the current density distribution within the heart (as compared to the non-patch transthoracic case), however, the chest paddles may be positioned on the chest. In an experimental study carried out in seven 83- to 109-kg calves, and with the usual paddle positions, we observed a marked decrease in efficacy in achieving transthoracic defibrillation with uniphasic rectangular waveforms when the patches were present compared to preimplantation efficacy.[32,33]

While our study was motivated by a problem observed in the first generation clinical system, the problem is generic in scope and one that deserves to be carefully evaluated as each new system is considered for general clinical use. Our primary suggested solution, always implanting defibrillator and patches at the same time, is only one of several ways of handling the problem.

Most of our additional important studies that

focused specifically on implanted defibrillators[34–42] were rooted in the more basic work described previously or to be discussed below. Furthermore, our more recent studies were frequently reported at about the same time that other research groups were reporting on broadly similar studies.

Uniphasic Transthoracic Defibrillation in the Calf

The mid-1970s saw a spirited controversy concerning the appropriate energy level for transthoracic defibrillation of human patients. Initiated by Tacker's article,[5] which suggested the need for higher energy, the controversy was joined by Pantridge and Adgey[43] and Crampton,[44] who made the opposite case.

The controversy motivated our group to construct the high energy research defibrillator described in an earlier section of this article and to switch from the dog to the 100-kg calf as the model for most of our experimental transthoracic work. The new model was chosen primarily because it approximated the weight of large human patients. Secondary considerations included the year-round availability of calves in mid-Missouri and the potential direct application of the studies to the implanted artificial heart program in which calves were extensively used.

Parenthetically, a side benefit of working with two or more species is that intuitively, at least, it increases one's confidence that the results can be extrapolated to human patients when they coincide and suggests caution when they diverge.

Families of curves of percent success versus pulse duration and delivered energy, derived from a study published in Circulation in 1977 and involving 3303 fibrillation-defibrillation episodes with uniphasic rectangular wave shocks,[45] are shown in Figures 21 and 22. The failure of member curves of these graphs to plateau at or near the 100% success level contrasts with our experience in dogs. In the same study, we found that in the calf, in contrast to the dog, the postdefibrillation period is often characterized by long periods in which ventricular activity is absent with only p waves evident in the electrocardiogram.

In another study, we found that even when scaled for weight difference, and although generally similar in response, it is clearly easier to

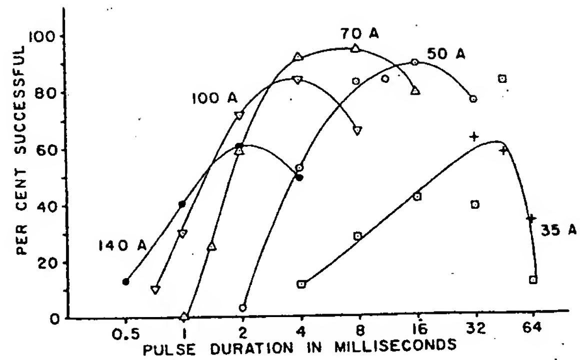

Figure 21. *Relation between per cent successful defibrillation and duration of transthoracic uniphasic rectangular wave shocks in 100-kg calves. (Reproduced with permission from the American Heart Association, Inc.[45])*

achieve consistent defibrillation in the dog model than in the calf with uniphasic rectangular shocks.[46]

A 6000-episode study of the defibrillation efficacy in 100-kg calves of truncated and untruncated exponential waveforms varying from 50- through 200-A initial current, 220 through 660 J "stored" energy, and having truncation levels of 0 through 45 A published in 1980[47] yielded results that, when scaled for subject weight and except for

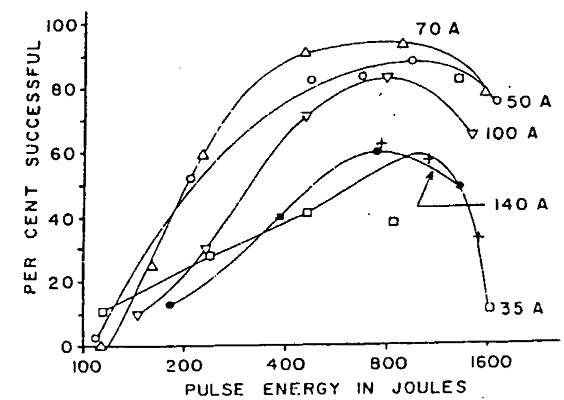

Figure 22. *Relation between per cent successful defibrillation and energy content of transthoracic unishasic rectangular wave shocks in 100-kg calves. (Reproduced with permission from the American Heart Association, Inc.[45])*

the two divergent factors mentioned above, generally paralleled those found in an earlier similar study in dogs.[18] In particular, the refibrillation phenomenon associated with a slowly decreasing tail was again clearly demonstrated.

In a 1982 study involving a rather complicated protocol, we carried out a 1200-episode investigation concerning the efficacy of relatively low energy uniphasic rectangular wave shocks delivered at 15-second intervals in defibrillating 100-kg calves.[48] When compared with the results from an earlier study,[45] we found little difference in overall efficacy between a defibrillation strategy that utilized a shock of optimal strength for trying to achieve single shock defibrillation and one that purposely used lower energy shocks with the expectation that repeated attempts to defibrillate would frequently be needed.

When combined with our earlier studies in dogs, these four articles, as will be discussed further in the next section, provided a credible basis for reconciling the apparently divergent perspectives of the advocates of low energy and of high energy defibrillation.

Scaling, Compound Units, Contour Graphs, and the Defibrillation Threshold

Although the consistent protocol and mode of data presentation, involving extensive databases, used in nearly all of our crucial transthoracic studies detailed above have yielded easily interpretable results and allowed meaningful comparisons from study to study, we have been concerned with developing improved approaches to the proper handling of research data from subjects of widely different size and with presenting data in an even more interpretable format.

Scaling

If a specified waveform of current is known to yield certain percent success in achieving defibrillation in one size of experimental animal of a given species, how should we scale our electrode system and current waveform to achieve the same percent success in a similarly shaped animal of the same species but different size?

Subject to certain assumptions, the question was answered on theoretical grounds in a paper presented at the 1975 Purdue Cardiac Conference,[49] in a 1979 article in Circulation,[50] and, with particular emphasis upon implanted systems, in a 1991 article.[51]

We concluded that if the linear dimensions of the electrodes are scaled by

$$d' = (m'/m)^{(1/3)}d \tag{1}$$

and the instantaneous current by

$$I' = (m'/m)^{(2/3)}I, \tag{2}$$

then the time varying current density vector at corresponding points within the animals will be everywhere identical (primed symbols refer to larger animals/systems; unprimed refer to smaller: d = linear dimensions, m = mass or weight, and I = instantaneous current).

If conditions specified by Equations 1 and 2 are satisfied, then the other parameters are related by

$$s' = (m'/m)^{(2/3)}s \tag{3}$$

$$V' = (m'/m)^{(1/3)}V \tag{4}$$

$$R' = (m'/m)^{-(1/3)}R \tag{5}$$

$$P' = (m'/m)P \tag{6}$$

$$U' = (m'/m)U \tag{7}$$

where s = electrode area, V = instantaneous voltage between electrodes, R = electrode-to-electrode resistance, P = instantaneous delivered power, and U = total delivered energy.

To the extent that the equality of the time varying current density vector at every corresponding point within two animals implies equal percent success in achieving defibrillation, Equations 1 and 2 tell us how to scale for equal percent success.

An experimental study in which six calves grew and survived to be studied at 50, 75, 100, 125, and 150 kg, subject to the conditions of Equations 1 and 2 did, indeed, serve to support the general validity of Equations 3–7.[50] However, while one 600-episode series (involving 70 A, 4-msec shocks when the animals were 100 kg) did support our hypothesis by yielding percent suc-

cess figures substantially independent of animal weight, another 600-episode series (50 A, 4-msec shocks when animals were 100 kg) failed to support our hypothesis that percent success would be independent of body weight. Despite an element of ambiguity represented by our experimental results, we continue to believe that the scaling scheme outlined above is informative and probably the best currently available.

Compound Units

In addition to its implications for the strategy for successful defibrillation in experimental subjects or patients of different sizes, scaling has important implications for how compound units should be used in graphs and tables that report experimental results.[51]

By rearranging each equation in the set, Equations 1–7 become

$$d'/m'^{(1/3)} = d/m^{(1/3)} \tag{8}$$

$$l'/m'^{(2/3)} = l/m^{2/3} \tag{9}$$

$$s'/m'^{(2/3)} = s/m^{2/3} \tag{10}$$

$$V'/m'^{(1/3)} = V/m^{(1/3)} \tag{11}$$

$$R'/m'^{-(1/3)} = R/m^{-(1/3)} \tag{12}$$

$$P'/m' = P/m \tag{13}$$

$$U'/m' = U/m. \tag{14}$$

These equations represent the relationships between the ratios of the parameters and the body weight (heart weight) raised to various powers that must exist if the current density vectors at corresponding points within the large and small subjects are to be the same. This, in turn, is presumably a necessary condition for the percent success to be dependent only on the values of the ratio and not upon the separate values of the parameters that make up the ratio in question.

The normalization scheme often used when considering total delivered energy is the same as Equation 14. Consequently, using the compound unit joules per kilogram, for example, is valid and compatible with our model. To the contrary, Equations 8–12 require something more than a simple ratio between the parameters of interest and weight. Therefore, such compound terms as amperes per kilogram or volts per kilogram, for example, are incompatible with our model and should probably be avoided.[51]

Contour Graphs

While utilizing the same database, the interpretation of defibrillation results as sketched in Figure 21, for example, can often be enhanced by a mode of presentation, initially conceived in 1966 by Alfred Dolan when he was a graduate student with our group, which we have termed the "contour graph."

Figure 23 is the contour graph that represents the same database as used in Figure 21. Its derivation is detailed in a 1979 American Heart Journal article.[52]

While drawn specifically for uniphasic rectangular wave shocks in 100-kg calves, this contour graph makes it quite evident that while the optimal energy may be quite high (for example, 800 J), much lower energies (for example, 200–400 J) still yield appreciable percent success figures; thus tending to reconcile the views of those who favored high energy defibrillation[5] and those who favored lower energy.[43,44] We think it quite likely that species differences exist that result in generally lower energy requirements for human patients.

Defibrillation Threshold

Although the dose response type of data collection and presentation (and the closely related contour graph) that we have used in nearly all of the work described above is easily interpretable and conceptually unambiguous, it is expensive in terms of investigator/technician time and of the number of research animals required. Furthermore, because of the large number of episodes usually required, the method ordinarily is not suitable for performance evaluation at the time defibrillation devices are implanted in human patients.

Consequently, in an attempt to reduce the effort needed to quantitate efficacy, many investigators have utilized a descriptor termed the "defibrillation threshold." For an idealized case in which the dose response curve is assumed to change from 0% to 100% probability of success with an infinitesimal increase in the independent variable, as suggested by the highly hypothetical

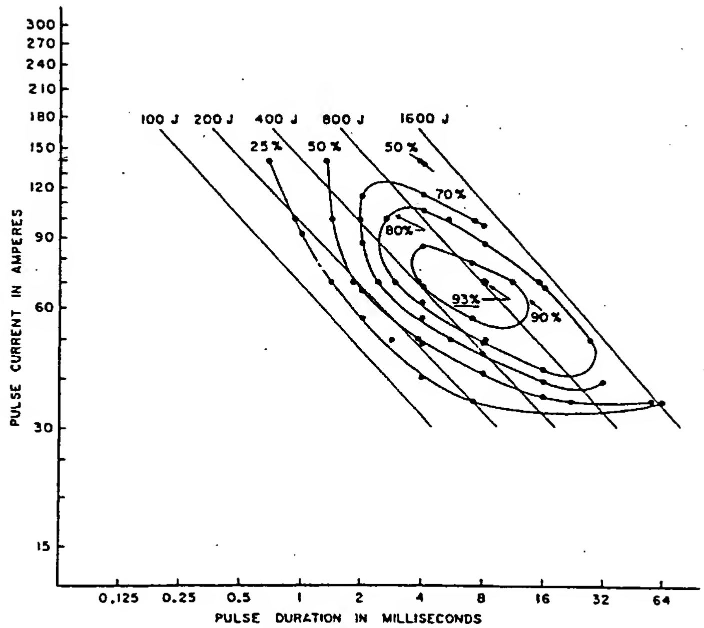

Figure 23. *Contour graph relating success in achieving transthoracic defibrillation in 100-kg calves to duration, current, and energy content of uniphasic rectangular wave shocks. (Reproduced with permission.[52])*

curve of Figure 24, the defibrillation threshold is widely understood to be the value of the independent variable at which the transition occurs.

But as demonstrated by sketches in this article, actual dose response curves are likely to (1) not exhibit a transitional jump in percent success,

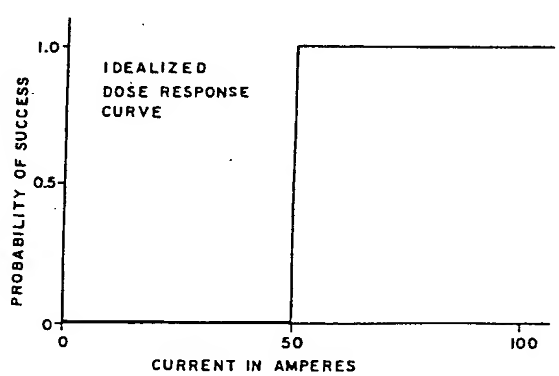

Figure 24. *Idealized dose response curve using current levels relevant to transthoracic defibrillation in 100-kg calves.*

(2) not peak at 100% success, and (3) eventually exhibit a decrease in percent success with increasing value of the variable of interest. Under such conditions, what do we mean by "defibrillation threshold"? The answer is far from clear with some authors using the term without specifying how it is to be evaluated and others providing an algorithm for its evaluation.

Bourland et al.[53] are to be credited with suggesting the most frequently used algorithm that involves fibrillating an animal and attempting to defibrillate with a specified generic current waveform anticipated to be near the assumed 50% success level. A success on the first try will be followed by another episode in which defibrillation is attempted with 20% less current than in the first case. The sequence is repeated with 20% additional decrements in current until failure is observed. The threshold is defined as average of the last two shocks. If the first try fails to defibrillate, the animal is defibrillated with a rescue shock and 20% more current is used in successive episodes until a success is achieved with the last

two current levels averaged to determine the threshold.

Motivated by early concerns expressed by Jerry Gold, our group was apparently the first to question the validity of the threshold concept from a theoretical perspective. Adapted from a 1985 abstract,[54] Figure 25 demonstrates the probability line spectrum of defibrillation threshold values that result from the application of Bourland's algorithm to a system with the simplified dose response curve shown when a shock that should be 50% successful is initially applied. Figure 26, reproduced from a later 1985 abstract,[55] demonstrates the derived threshold probability density spectrum when the initial shock is normally distributed around the 50% success level with standard deviations of 2.5 and 5 A.

The results shown in Figures 25 and 26 indicate that when there is a gradual transition between ineffective and effective shock levels, the thresholds derived using the Bourland approach may cover a broad range of current levels, thus supporting on theoretical grounds the work of Davy et al.[56] reported in 1984 that questioned, on experimental grounds, the validity of the threshold concept in the absence of a sharp transition in the dose response curve.

In full length articles[57,58] and abstracts,[59–61] we have further explained our reservations about the threshold concept and explored possible improved algorithms. While our work has resulted in increased awareness about the limitations of the threshold approach (as expressed in articles published by various authors), it has yielded only marginally improved algorithms.

Despite our work and the work of others in recent years, we continue to be uncomfortable about the status of the defibrillation threshold concept and look forward to the development of more satisfactory approaches to the twin problems it is intended to address.

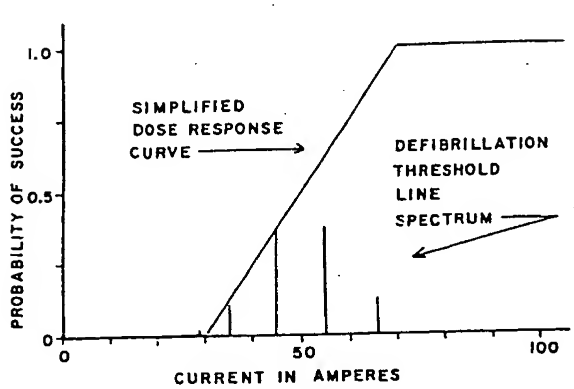

Figure 25. *Probability line spectrum of defibrillation threshold values associated with simplified dose response curve using current levels relevant to transthoracic shocks in 100-kg calves. (Adapted with permission.[54])*

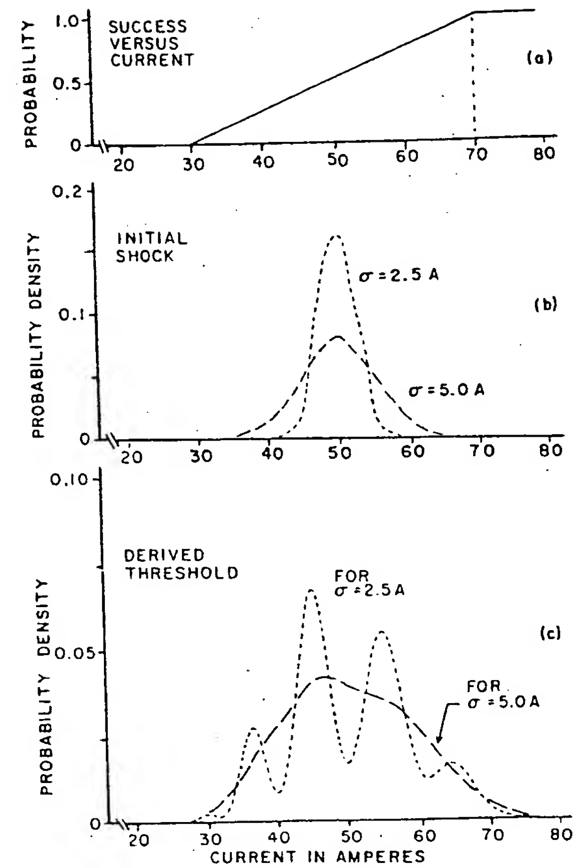

Figure 26. *Threshold probability density spectrum using current levels relevant to transthoracic shocks in 100-kg calves. (Reproduced with permission.[55])*

Biphasic Transthoracic Defibrillation in the Calf

In 1983/1984 our group published three articles reporting extensive studies concerning the

transthoracic defibrillation of 100-kg calves with biphasic waveforms.[62–64] When considered in conjunction with two earlier studies by our group involving uniphasic rectangular[45] and uniphasic exponential waveforms,[47] the data clearly suggested the appreciable and general superiority of biphasic over uniphasic waveforms. This outcome served to motivate our group and other investigators to undertake studies involving biphasic shocks in implanted electrode systems as well as for transthoracic use.

Symmetrical One Cycle Biphasic Rectangular Waveform

From 2760 fibrillation-defibrillation episodes in 100-kg calves, the efficacy in reversing ventricular fibrillation of 30-second duration with symmetrical one cycle biphasic rectangular shocks was determined for 23 pulse amplitude-pulse duration combinations in a 1983 article published in the IEEE Transactions on Biomedical Engineering.[62] Percent success versus pulse duration and pulse amplitude and percent success versus delivered energy and pulse amplitude are shown in Figures 27 and 28, respectively. The explicit meaning of the duration parameters for uniphasic and biphasic waveforms is shown in Figure 29.

While a comparison of the family of curves in Figure 27 with that in Figure 21 and the family of curves in Figure 28 with that in Figure 22 demonstrates the superiority of the biphasic waveform, the comparison is further enhanced by the 90% success contour graph for the two categories of waveforms that is sketched in Figure 30. These various graphs indicate that in the 100-kg calf model, at least, biphasic waveforms yield a higher peak success level at an appreciably lower energy level than do uniphasic wave shocks and that the range of parameters for a given level of success is much broader for biphasic than for uniphasic shocks.

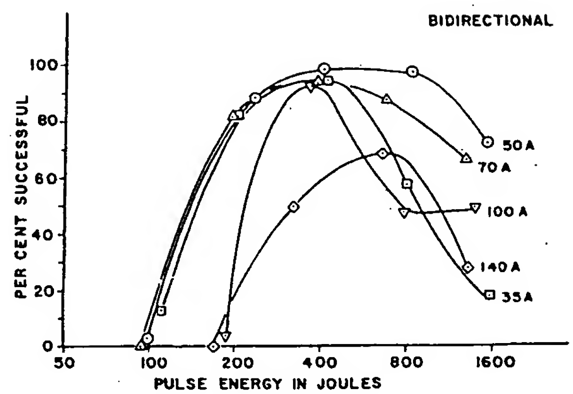

Figure 28. *Relation between per cent successful defibrillation and energy content of transthoracic biphasic rectangular wave shocks in 100-kg calves. (Reproduced with permission.[62] © 1983 IEEE.)*

Asymmetrical One Cycle Biphasic Rectangular Waveform

In a 2640-episode calf study published in a 1984 Cardiovascular Research article,[63] we dem-

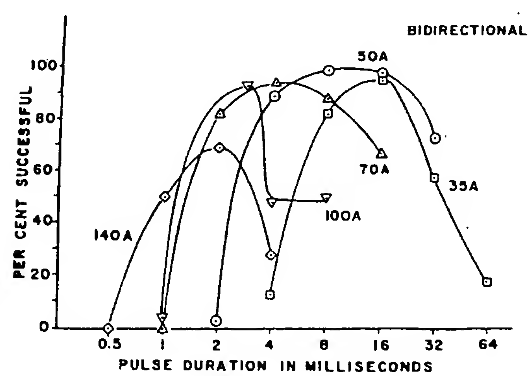

Figure 27. *Relation between per cent successful defibrillation and duration of transthoracic biphasic rectangular wave shocks in 100-kg calves. (Reproduced with permission.[62] © 1983 IEEE.)*

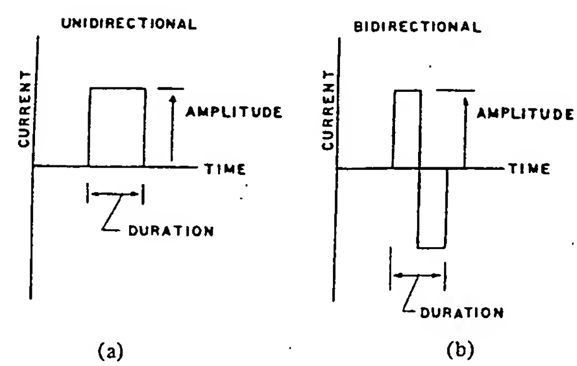

Figure 29. *Explicit meaning of the duration parameter in both uniphasic and biphasic study in calves. (Reproduced with permission.[62] © 1983 IEEE.)*

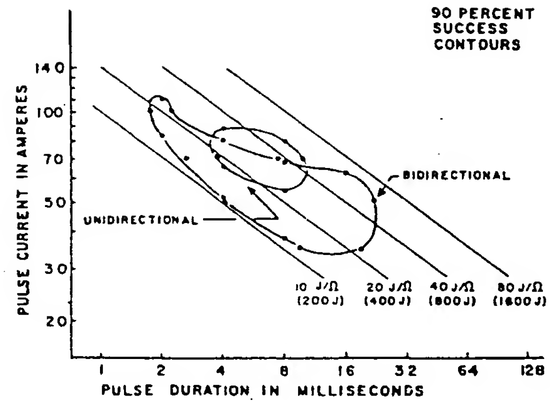

Figure 30. *Contour graph relating duration, current, and energy content of uniphasic and biphasic rectangular wave shocks that are 90 percent successful in the transthoracic defibrillation of 100-kg calves. (Reproduced with permission.[62] © 1983 IEEE.)*

onstrated that the superiority of symmetrical biphasic waveforms in achieving defibrillation was shared by certain important categories of asymmetrical biphasic waveforms. On an energy basis, appropriate waveforms of the generic category sketched in Figure 31, with the leading and lagging portions of equal duration and the lagging portion smaller than, but an appreciable fraction of (for example, > ¼) the amplitude of the leading portion, are at least as good as symmetrical shocks.

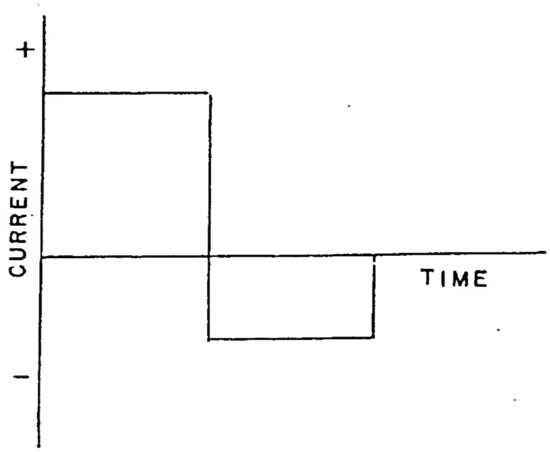

Figure 31. *Category of asymmetrical biphasic waveforms considered in a 1984 Cardiovascular Research article.[63]*

A limited later study indicated that reversing the time order of the large and small amplitude shocks resulted in a drastic decrease in efficacy.[65]

One Cycle Biphasic Truncated Exponential Waveform

Although biphasic rectangular shocks are convenient for research purposes because the parameters can be unambiguously specified and interpreted, they are difficult to generate in clinical sized apparatus. Consequently, in a 960-episode study published in the 1984 Transactions American Society for Artificial Internal Organs,[64] we evaluated the efficacy of symmetrical and asymmetrical biphasic truncated exponential waveforms that could be easily generated in the transthoracic defibrillation of 100-kg calves.

In carrying out the study, we selected eight exponential waveforms that were related in a manner shown in the sketch of Figure 32 to biphasic rectangular waveforms previously studied.[62,63] The results indicated that the truncated exponential shocks were well behaved with the percent success figures always falling within, or very close to, the range of values found for the associated biphasic rectangular waveforms. This allows one to predict approximately biphasic exponential waveform performance from the rectangular waveform database. Furthermore, the most successful of the biphasic truncated exponential waveforms evaluated (100%)[64] was equivalent to the most successful biphasic rectangular waveform (100%)[63] and superior to the most successful uniphasic rectangular (93%)[45] and uniphasic truncated exponential (94%)[47] waveforms in achieving defibrillation in 100-kg calves.

Other Biphasic and Multiphasic Waveforms

In addition to the three extensive biphasic transthoracic studies in 100-kg calves outlined above and which form the core of the case for the superiority of biphasic shock defibrillation, we carried out three transthoracic studies[66–68] of a more limited nature in 100-kg calves.

One tended to reinforce and generalize the case for the superiority of biphasic defibrillation.[66] Using a circuit based upon the topology described by Negovsky et al.,[7] we interlaced 120 episodes involving the quasisinusoidal biphasic waveform shown in Figure 33 with 120 episodes involving

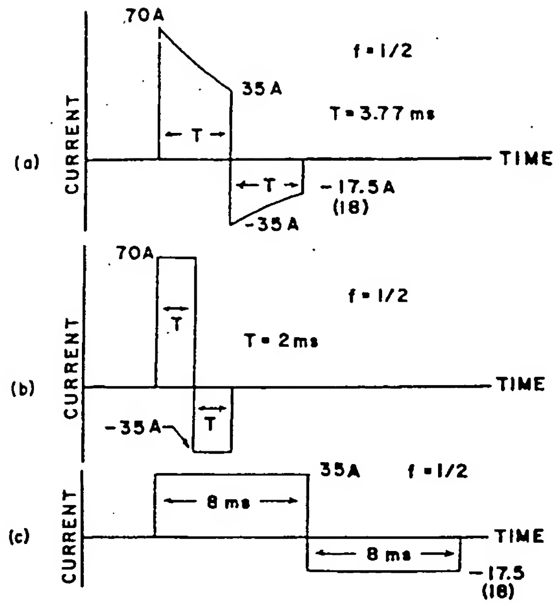

Figure 32. *Category of waveforms that have the same fractional value of undershoot and deliver the same energy to a given load. One of the biphasic exponential waveforms evaluated (a), biphasic rectangular waveform having current amplitude of leading half-cycle equal to the initial current value of leading half-cycle of exponential waveform (b), and biphasic rectangular waveform having current amplitude of leading half-cycle equal to final value of current in leading half-cycle of exponential waveform (c). (Reproduced with permission.[64])*

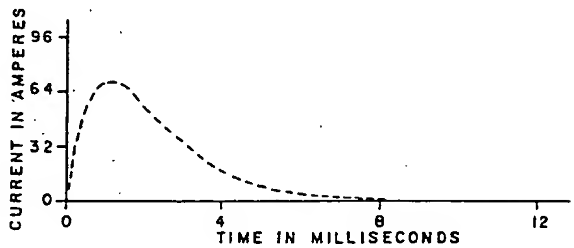

Figure 34. *Critically damped uniphasic waveform used in comparative study with waveform shown in Figure 33. (Reproduced with permission.[66])*

the critically damped uniphasic waveform sketched in Figure 34. With the delivered energy being about 200 J in both cases, the quasisinusoidal biphasic waveform was 88% successful while the critically damped uniphasic waveform was only 37% successful. In contrast to the rectangular and truncated exponential waveforms previously discussed, this biphasic waveform may be easily generated by mechanical relay switching. Unfortunately, circuit efficiency is quite low.

In another limited study,[67] 120 episodes with the biphasic waveform represented by the solid curve in Figure 35 were interlaced with 120 episodes with a triphasic waveform created by adding the dashed curve shown in Figure 35 to the biphasic waveform. For these purposely selected supraenergy shocks (two to three times optimal), significant difference in percent successful defibrillation was not observed, although the triphasic waveform did yield a modest reduction in the time required for the return of normal sinus rhythm.

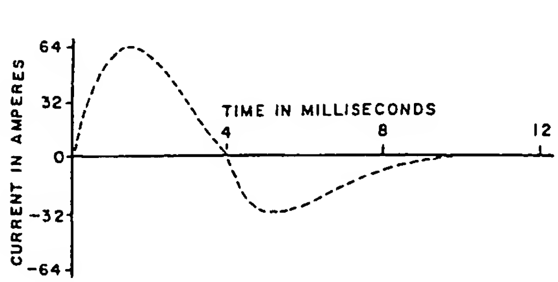

Figure 33. *Quasisinusoidal biphasic waveform used in transthoracic study of defibrillation of 100-kg calves. (Reproduced with permission.[66])*

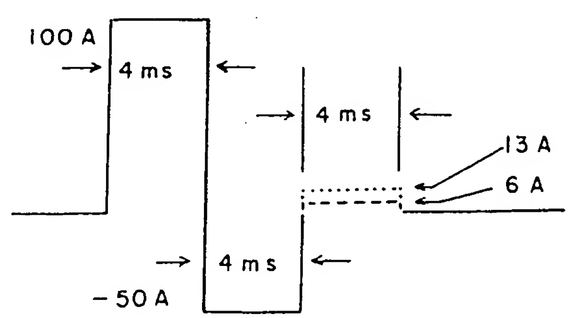

Figure 35. *Biphasic and triphasic waveforms used in transthoracic defibrillation of 100-kg calves. (Reproduced with permission.[67])*

Similar comparative results were observed when the lagging portion of the triphasic waveform was increased to 13 A as shown by the dotted curve of Figure 35.

In the third limited study,[68] 120 episodes with a much underdamped, and untruncated, multiphasic sinusoid (0 crossings separated by 4.05 msec; successive peaks of +58, −16.5, +4.7 . . . A) were interlaced with 120 episodes using a known effective biphasic asymmetrical rectangular waveform (leading half cycle of +38 A, 4 msec, and a lagging half cycle of −18.5 A, 4 msec). Both waveforms delivered purposely suboptimal levels of approximately 150 J. The percent successful defibrillation achieved (73% for multiphasic, 76% for biphasic) did not differ significantly.

Like the quasisinusoidal biphasic waveform discussed above,[66] this multiphasic waveform is easily generated by a mechanical relay switch.

Significance of Biphasic Waveform Studies

It is evident that not every biphasic waveform is superior to every uniphasic waveform for achieving ventricular defibrillation. As just one obvious example, a uniphasic rectangular waveform of appropriate amplitude and duration is far more effective than either very short or very long biphasic rectangular shocks, regardless of amplitude.

Nevertheless, to the extent that the experimental results in animals may be extrapolated to human patients, the data generated in our core studies,[62–64] when combined with contributions from later studies by our own group and other investigators, support the growing interest in using biphasic (or perhaps other multiphasic) waveforms for implantable and transthoracic defibrillators designed for clinical application.

Funding the Program

During its first two decades, our program was funded mostly by the American Heart Association, its Missouri affiliate, and the National Institutes of Health. Starting in the early 1980s, corporate support primarily from the Physio-Control Corp. (Redmond, WA, USA) and, later, from Cardiac Pacemakers, Inc., constituted an appreciable portion of our funding.

Future

As manufacturers bring devices designed to manage multiple kinds of arrhythmias to the market, we anticipate that the field of ventricular defibrillation will continue to be active and exciting. Furthermore, we expect that basic research by several groups will begin to yield a more fundamental understanding of the fibrillation/defibrillation process on a cellular and whole organ basis.

For our part, we hope to play a role in helping manufacturers to correctly interpret the databases presently available in order to optimize the efficacy of the newer waveforms and to carry out apparatus intensive studies focused at evaluating several fundamentally new and different approaches to achieving ventricular defibrillation.

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